Immunoserological Profile of Celiac Disease among Iraqi Children and Adults with Type 1 Diabetes Mellitus

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Original Article

ABSTRACT

Background:
Celiac disease is also often found in people with type 1 diabetes mellitus and is thought to share common genetic and immunologic pathways, so it is common to be diagnosed with both conditions. These conditions may coexist and exacerbate clinical conditions and are rarely investigated in Iraqi populations.
Aims:The aim of the study was to measure the prevalence of celiac disease in Iraqi children and adult patients with type 1 diabetes mellitus and its relationship with pancreatic autoantibodies (glutamic acid decarboxylase antibody (GADA) and islet cell antibody (ICA)).
Materials and Methods:
We conducted a case–control study of 69 patients with type 1 diabetes mellitus and 50 healthy controls. Serum samples were analyzed for anti-tTG IgA using ELISA, while GADA and ICA were detected using ELISA and immunofluorescence techniques, respectively. We performed statistical analyses using SPSS software version 26.
Results:
Anti-tTG positivity was significantly higher in patients with diabetes (21.7%) compared with controls (6%) ($P = 0.018$). GADA and ICA were significantly elevated in patients ($P < 0.0001$ and $P = 0.005$, respectively). No significant association was found between anti-tTG and either GADA ($P = 0.292$) or ICA ($P = 0.066$), although a trend was observed with ICA.
Conclusions:
Celiac disease-related autoimmunity is more prevalent in patients with type 1 diabetes mellitus, supporting routine screening. However, pancreatic and intestinal autoimmunity may develop through partially independent mechanisms.

Keywords: Type 1 diabetes mellitus; Celiac disease; Anti-tTG; GADA; ICA.

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INTRODUCTION:

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease that is associated with progressive loss of pancreatic β -cells that results in complete insulin deficiency and permanent reliance on exogenous insulin therapy. It is most common in children and young adults and is one of the most prevalent endocrine disorders globally(1). T1DM pathogenesis involves a complex interplay of genetic predisposition, environmental factors, and immune-mediated pathways that lead to the production of autoantibodies such as glutamic acid decarboxylase antibodies (GADA) and islet cell antibodies (ICA). These immunological biomarkers indicate continuous destruction of β-cells, and they are extensively employed in the diagnosis and monitoring of the disease(2,3).

Celiac disease (CD) is yet another immune-related disease that is marked by a faulty immune reaction to gluten in the diet of persons who are genetically predisposed. The disease results in chronic inflammation of the small intestinal mucosa and villous atrophy, malabsorption and a wide range of gastrointestinal and extraintestinal symptoms (4). Diagnosis is primarily made based on serological tests for anti-tissue transglutaminase (anti-tTG) antibodies and intestinal biopsy is then used to confirm the diagnosis (5).

T1DM and CD are increasingly being observed, and many studies have shown that there is a higher prevalence of CD in people with T1DM when compared to the general population. Many of the genetic factors are shared, in particular human leukocyte antigen (HLA) haplotypes, such as HLA-DQ2 and HLA-DQ8, which are associated with predisposition to a number of autoimmune diseases. In addition to genetic overlaps, common immune-pathogenic mechanisms such as activation of T-cells, disruption of cytokine balance and failure of immune tolerance also contribute to the co-occurrence of the two diseases (6,7).

Clinical relevance and management of the comorbidities of T1DM and CD is of clinical relevance. Poor glycemic control, growth retardation in children, micronutrient deficiencies, and a higher risk of long-term complications may occur in diabetic patients who are undiagnosed with CD. For people with both conditions, however, following a gluten-free diet may improve metabolic control and health outcomes. Therefore, it is important to identify CD early in patients with T1DM (8,9).

This association is known throughout the world, but knowledge of populations in the Middle East, particularly in Iraq, is limited. Variations in genetics, diet, environment and health care access may affect the incidence and characteristics of CD in T1DM patients between regions (10). Furthermore, there is still insufficient knowledge about the correlation between pancreatic autoantibodies (including GADA and ICA) and celiac-specific antibodies (anti-tTG) and literature reports mixed results about the correlation between the two (11).

In this regard, the immune status of Iraqi T1DM patients to CD should be evaluated to gain a better insight into the burden and nature of this comorbidity (12). The prevalence of anti-tTG antibodies, along with their association with other autoimmune markers, can be informative, can aid in identifying immunopathological mechanisms involved in the development of the disease, and can lead to identifying high-risk individuals who will benefit from periodic screening (13).

The present study was designed to investigate the prevalence of celiac disease in T1DM patients in children and adults in Iraq and to examine the relationship between the CAAs (anti-tTG) and pancreatic autoantibodies (GADA and ICA) and to evaluate the immunological relationship between the two autoimmune diseases.

MATERIALS AND METHODS:

This case-control study was conducted over two years, from January 2024 to January 2026, at specialized diabetic and pediatric clinics in Iraq. The sample consisted of 69 children and adolescents who had T1DM and 50 age- and sex-matched individuals who appeared healthy as the control group. The diagnosis of T1DM was made according to the usual clinical criteria, such as the symptoms of hyperglycemia, the level of fasting blood glucose, and the necessity of insulin therapy. Inclusion criteria were children and young people aged 3 to 30 years with confirmed T1DM, and exclusion criteria were other autoimmune diseases, chronic infections, or systemic diseases that could interfere with immunological measurements.

All the participants were sampled under aseptic conditions (5 mL of venous blood). Serum was separated by centrifugation at 3000 rpm and stored at -20C until analysis. The presence of IgA antibodies against tissue transglutaminase (anti-tTG) in serum samples was screened by solid-phase enzyme-linked immunosorbent assay (ELISA) (Aeskulisa tTG-A, Germany), which can detect both qualitative and quantitative IgA antibodies against tissue transglutaminase and is commonly used in the diagnosis and management.

We also measured serum concentrations of diabetes-associated autoantibodies, such as GADA, using ELISA kits (EUROIMMUN, Germany), and determined ICA by indirect immunofluorescence (EUROIMMUN, Germany). All laboratory procedures were carried out according to the manufacturers' instructions.

Statistical analysis:

Data were analyzed using SPSS software (version 26).

Data were presented as frequencies and percentages for categorical variables. The relationship between categorical variables was tested by the Chi-square ($\chi 2$) test with Yates correction in case of necessity. For continuous variables, data were indicated in the form of mean and standard deviation (SD), and an independent t-test was used for normally distributed data; the Mann-Whitney U test was used for non-normally distributed variables. A P-value of 0.05 was considered statistically significant.

Ethical approval:

The research was carried out in compliance with the ethical principles of the Declaration of Helsinki, and informed consent of all the subjects or their guardians was obtained before sample collection.

RESULTS

Age Distribution among Patients with T1DMand Healthy Controls

Table 1 showed that the mean age of patients with T1DM and celiac disease was 14.42 ± 6.41 years, with a range of 3.5-30 years. Comparatively, the control group had a slightly higher mean age of 17.73 ± 7.71 years, with a wider range of 1-32 years. Though the control group seemed to be older on average, the fact that there is overlap in the age range of both groups is an indication of a relatively similar age distribution. These results suggest that both cohorts captured the age difference well, reducing the chance of age-related confounding in further analyses.

Table 1.Comparative analysis of age characteristics between patients with celiac disease and type 1 diabetes mellitus and matched controls

Group	N	Minimum	Maximum	Mean+SD
Patient age	69	3.5 year	30 year	14.42+6.41
Control age	50	1 year	32 year	17.73+7.71

Sex Distribution among Patients and Control Groups

These sex distribution percentages in Table 2 revealed that male patients made up 52.17% (n = 36), whereas femalepatients comprised 47.82% (n = 33). Men constituted 44% (n = 22) and women 56% (n = 28) in the control group. Statistical analysis showed no significant difference in sex distribution between controls and patients ($\chi^2 = 0.78$, $P > 0.05$). These results indicate that the two groups were similar regarding sex distribution, implying that the aspect of sex is not likely to confound the study results.

Table 2. Comparison of sex distribution between individuals with type 1 diabetes mellitus and celiac disease and healthy controls

Group			Percent	χ2- Pvalue
Patient	Male	36	52.17%	0.78, >0.05
	Female	33	47.82%	
	Total	69	100%	
Control	Male	22	44 %	
	Female	28	56 %	
	Total	50	100%	

Distribution of Anti-tTG Antibodies among Patients with Diabetes and Control Group

We analyzed anti-tTG antibody distribution, and Table 3 shows that the seropositivity rate among patients with diabetes was significantly higher than in controls. In the patient group, 21.73% (n = 15) were positive for anti-tTG antibodies, and 78.26% (n = 54) were negative. Conversely, the control group (n = 3) recorded only 6% (n = 3) positive anti-tTG results, with a majority (94%, n = 47) recording negative results. The two groups differed significantly ($\chi^2 = 5.55$, $P = 0.018$). These results imply that T1DM and a higher prevalence of autoimmunity related to celiac disease, as evidenced by high levels of anti-tTG antibodies, are closely related.

Table 3. Comparison of seropositivity rates of anti-tissue transglutaminase (anti-tTG) antibodies between patientswith type 1 diabetes mellitusand healthy controls

			Anti-tTG		Total	C.S. Pvalue
			Neg.	Pos.		
group	Patients with Diabetes	Count	54	15	69	5.55, =0.018
		% within group	78.26%	21.73%	100%	
	Control	Count	47	3	50	
		% within group	94%	6%	100%	
Total		Count	101	18	119	

Association betweenSex and Anti-tTG Antibody Status in Patients with Diabetes

The correlation between sex and anti-tTG antibody status among patients with diabetesin Table 4was analyzed, which did not show any statistically significant correlation. Among men, 19.44% (n = 7/36) were positive for anti-tTG antibodies, while 80.56% (n = 29/36) were negative.

Similarly, in women, 24.24% (n = 8/33) tested positive, whereas 75.76% (n = 25/33) were negative. The overall distribution showed that anti-tTG positivity was slightly higher in women than in men, but this difference did not reach statistical significance (χ^2 = 0.23, P > 0.05). These results imply that sex is not a major factor that determines the occurrence of autoimmunity in patients with T1DM who have celiac disease.

Table 4. Evaluation of the relationship between sex distribution and anti-tissue transglutaminase seropositivity among patients with type 1 diabetes mellitus

	Group		Anti-tTG		Total	C.S. Pvalue
			Neg.	Pos.		
Sex	Male	Count	29	7	36	0.23, >0.05 NS
		% of total	42.02%	10.14%	52.17%	
	Female	Count	25	8	33	
		% of total	36.23%	11.59%	47.82%	
Total		Count	54	15	69	
		% of total	78.26%	21.74%	100%	

Distribution of GADA among Patientswith Diabetes and Control Group

The GADA distribution analysis showed a significantly higher seropositivity rate in patients with diabetes than in the control group. Among patients, 65.2% (n = 45) tested positive for GADA, while 34.8% (n = 24) were negative. By contrast, everybody in the control group (100, n = 50) was negative for GADA; not a single positive individual was identified. The statistical difference between the two groups was very significant (χ^2 = 49.7, P < 0.0001, Yates-corrected). The results indicate that GADA positivity is strongly related to T1DM and can be used as a significant immunological biomarker in the pathogenesis and diagnosis of the disease, as shown in Table 5.

Table 5. Comparison of glutamic acid decarboxylase antibodies (GADA) seropositivity between patients with Type 1 diabetes mellitus and healthy controls

			GADA		Total	C.S. Pvalue
			Neg.	Pos.		
Group	Disease	Count	24	45	69	49.7, <0.0001 HS, Yates-corrected
		% within group	34.8%	65.2%	100%	
		% of Total	30%	56.25%	86.25%	
	Control	Count	50	0	50	
		% within group	100%	0%	100%	
		% of Total	%	0%	%	
Total		Count	74	45	119	
		% within group	%	%	100%	
		% of Total	%	%	100%	

Distribution of ICA among Patients with Diabetes and Control Group

The ICA distribution analysis in Table 6showed a markedly higher prevalence of seropositivity in patients with diabetes than in the control group. Among patients, 17.4% (n = 12) tested positive for ICA, while 82.6% (n = 57) were negative. Conversely, none of the control group were positive for ICA (0%). The two groups had a significant difference (χ^2 = 7.85, P = 0.005, Yates-corrected). These results show a significant correlation between T1DM and ICA positivity, supporting its use as an immunological biomarker associated with autoimmune conditions in patients.

Table 6. Comparative analysis of ICA seropositivity between patients with Type 1 diabetes mellitus and healthy controls

			ICA		Total	C.S. Pvalue
			Neg.	Pos.		
Group	Disease	Count	57	12	69	7.85, =0.005 HS, Yates-corrected
		% within group	82.6%	17.4%	100%	
		% of Total	71.25%	15%	86.25%	
	Control	Count	50	0	50	
		% within group	100%	0%	100%	
		% of Total	%	0%	%	
Total		Count	107	12	119	
		% within group	%	%	100%	
		% of Total	%	%	100%	

Association between GADA and Anti-tTG IgA Antibody Status in Patients with Diabetes

Table 7 shows a non-statistically significant association between GADA and anti-tTG IgA antibody status in patients with diabetes. Among GADA-negative individuals, 12.5% (n = 3/24) were anti-tTG IgA positive, and 87.5% (n = 21/24) were negative. On the same note, in GADA-positive individuals, 26.7% (n = 12/45) were positive for anti-tTG IgA, and 73.3% (n = 33/45) were negative. Although a higher percentage of anti-tTG positivity was found in GADA-positive patients, the difference was not statistically significant (Pearson χ^2 = 1.84, P = 0.292; Mantel–Haenszel corrected). These results imply that GADA positivity is not substantially linked to autoimmune disease related to celiac disease in this group.

Table 7. Evaluation of the relationship between glutamic acid decarboxylase antibodies (GADA) and anti–tissue transglutaminase (tTG IgA) seropositivity among patients with type 1 diabetes mellitus

Parameter	Responding	Count & Percent	tTG IgA antibody		Total
			Neg.	Pos.	
GADA	Neg.	Count	21	3	24
		% of Total	30.4%	4.3%	34.7%
	Pos.	Count	33	12	45
		% of Total	47.8%	17.4%	65.2%
Total		Count	54	15	69
		% of Total	78.3%	21.7%	100%
C.S.Pvalue		Pearson chi-square=1.84 P value=0.292		Mantel-Haenszel corrected	

Association between ICA and Anti-tTG IgA Antibody Status in Patients with Diabetes

The association between ICA and anti-tTG IgA antibody status in patients with diabetes showed no statistically significant relationship, but a tendency toward such an association was observed. Among ICA-negative individuals, 17.5% (n = 10/57) were positive for anti-tTG IgA, while 82.5% (n = 47/57) were negative. Conversely, 41.7% (n = 5/12) of ICA-positive patients had anti-tTG IgA, as compared with 58.3% (n = 7/12) who were negative. Although the anti-tTG positivity was higher in ICA-positive individuals, this was not statistically significant (Pearson χ^2 = 3.39, P = 0.066). These results indicate that ICA may be involved with autoimmunity due to celiac disease, but more extensive research is necessary to determine this connection, as shown in Table 8.

Table 8. Evaluation of the relationship between islet cell antibodies (ICA) and anti–tissue transglutaminase (tTG IgA) seropositivity among patients with type 1 diabetes mellitus

Parameter	Responding	Count & Percent	tTG IgA antibody		Total
			Neg.	pos.	
ICA	Neg.	Count	47	10	57
		% of Total	68.1%	14.5%	82.6%
	Pos.	Count	7	5	12
		% of Total	10.1%	7.3%	17.4%
Total		Count	54	15	69
		% of Total	78.3%	21.7%	100%
C.S.P-value			Pearson Chi-square=3.39 P value=0.066		

DISCUSSION:

The present study provides useful information on immunological interaction between T1DM and CD particularly for the analysis of serological markers (anti-tTG, GADA and ICA). This study's finding that anti-tTG antibody levels are significantly higher in patients with diabetes than in controls highlights the strong association between T1DM and celiac related autoimmunity. This finding is consistent with several epidemiological studies showing that the prevalence of CD is higher among T1DM patients, presumably attributed to the shared genetic risk of these two haplotypes, HLA-DQ2 and HLA-DQ8 (14,15). These haplotypes allow for defective antigen presentation that results in a pro-inflammatory immune cross reactivity of both the pancreatic β-cells and intestinal tissue.

The mechanism of chronic immune activation in T1DM may lead to susceptibility to other autoimmune responses, such as the production of anti-tTG antibodies. Diabetic patients may also have increased exposure of antigens to gluten, leading to immune responses in CD, due to mucosal barrier dysfunction (16,17). This complements the literature demonstrating that systemic inflammation and immune dysregulation play a key role in the co-occurrence of auto-immune diseases (18). However, other reports have reported low or absent correlation between T1DM and CD (19), which could be due to differences in population genetics, gluten exposure, and diagnostic criteria.

The positivity rate of the GAD antibody was also found to be significantly high in patients with diabetes and zero in controls in the GADA distribution analysis, reinforcing its role as a hallmark autoantibody in the pathogenesis of T1DM. This is in line with previous reports that GADA is an autoimmune process against pancreatic β-cells and a good diagnostic biomarker (20,21). Although this was strongly correlated, the fact that the current study did not show any significant correlation between GADA and anti-tTG antibodies implies that the subsequent development of pancreatic and intestinal autoimmunity may follow slightly different mechanisms. This is consistent with the finding that although both diseases are genetically determined, the immunological factors and effector mechanisms might be different (22,23).

Similarly, ICA positivity was significantly associated with patients with diabetes, but not with controls, further indicating the autoimmune nature of T1DM. The correlation between ICA and anti-tTG antibodies, however, is borderline non-significant, indicating a lower or less direct correlation between islet cell autoimmunity and immune responses that result in the development of celiac disease. In part, this is consistent with the previous reports suggesting a variable relationship between the ICA and

CD markers (24). The statistical non-significance might be due to the small sample size and/or to the time lag between the appearance of antibody and the onset of the disease (anti-tTG appears later in the disease process than ICA, after gluten has been consumed and intestinal damage has occurred) (25).

No significant sex differences were found between the patients and controls in the sex distribution analysis, which indicates that sex does not seem to be a confounder for the immunological associations found. This is in keeping with other studies which have also reported a similar sex ratio in children and young adults with T1DM (26). However, other reports have suggested that there might be a slightly greater prevalence of CD in women, possibly due to the role of hormones in regulating immune response (27). Sample characteristics and local differences could be responsible for this lack of trend in this study.

Interestingly, age ranges overlapped between patients and controls, which suggests that ages were well matched and not excessively confounded by age. The age distribution of people may also affect the maturity of the immune system and the production of autoantibodies, thus supporting the validity of observed associations (28).

It is also possible that the lack of significant correlation between GADA and anti-tTG and between ICA and anti-tTG is due to so-called autoimmune clustering, in which several autoimmune diseases tend to occur together, but they are not necessarily serologically related. This is observed in autoimmune polyglandular syndromes, where different autoimmune diseases occur simultaneously, but with different types of autoimmune reactions (29). Furthermore, the gut and pancreatic microenvironment can have selective immunomodulatory effects on immune functions of the gut and pancreas (30).

However, some methodological variations in some previous studies and the present study could result in different differences between the studies, including variation in assay sensitivity, antibody cutoff values and study design. For instance, discrepant results for anti-tTG detection by ELISA assay versus other immunoassays may impact reported prevalence. Furthermore, CD prevalence is also seen to differ depending upon geographical and ethnic origin, and studies have shown that prevalence of CD in T1DM patients varies from region to region (31).

CONCLUSION:

Finally, the current study confirms the strong link between T1DM and autoimmunity related to celiac disease, based on the high rate of anti-TTG seropositivity. The absence of significant linkage between the different autoimmune markers, however, (GADA versus anti-tTG) suggests that these autoimmunity processes may be distinct, but parallel. The results highlight the need for regular screening for CD in children with T1DM and point to the need for larger-scale studies to further characterize the intricate immunological relationships that underlie autoimmune comorbidities.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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